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Spatial and temporal progressions of spatial statistical moments in linear chromatography

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Abstract

Generalizations of existing models of chromatography allow the spatial and temporal progressions of all spatial statistical moments in linear chromatography to be given as the solution to a set of ordinary differential equations. Basic strategies of simplifying these equations are described. © 2001 Published by Elsevier Science B.V.

Keywords: Spatial statistical moments; Statistical analysis; Mathematical modelling

1. Introduction

One of the most fundamental models of chromatographic behavior is based on a one-dimensional system where migration is modeled as a bulk displacement and dispersion is modeled as an effective diffusion process [1]. The basic assumption governing this model is that

$$j(x, s) = v(x, s)c(x, s) - D(x, s) \frac{\partial c}{\partial x}(x, s) \quad (1)$$

where j is flux, v is the displacement velocity, c is concentration, D is the effective Fick diffusion coefficient, x is longitudinal space, and s is time. Applying the equation of continuity to Eq. (1) gives the partial differential equation that is the current model of chromatography under spatially and temporally varying conditions [1,2]:

$$\frac{\partial c}{\partial s}(x, s) = \frac{\partial}{\partial x} D(x, s) \frac{\partial c}{\partial x}(x, s) - \frac{\partial v c}{\partial x}(x, s) \quad (2)$$

This equation is essentially Fick's Second Law with an additional term to account for the bulk displacement of solute. Based on this equation, Blumberg has been able to describe generally the spatial variance of a zone migrating through a linear medium under temporally and spatially changing conditions [2]. This theory gives the progression of spatial variance as the solution to the following ordinary differential equation:

$$\frac{d\sigma^2}{dz} = H(z, t) + 2\sigma^2 \frac{\partial \ln u}{\partial x}(z, t) + \sigma^2 \frac{\partial H}{\partial x}(z, t) \frac{\partial \ln u}{\partial x}(z, t) \quad (3)$$

where σ^2 is the spatial variance of the zone, z is the spatial zone centroid, t is the time required for the centroid to reach position z , H is the local height equivalent of a theoretical plate (local HETP) [2], and u is the net solute velocity due to displacement

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and any spatial variation of diffusivity [3]. Less general forms of Eq. (3) have also been derived [3–6], and these equations have been used successfully to predict spatial zone variances in linear solvent strength gradient liquid chromatography [4,7] and reversed-phase alternate-pumping recycle liquid chromatography [6,8,9]. However, these theories address the progression of spatial zone *variance* only (i.e. the second normalized central moment). Higher order moments, which describe the skew, excess, and other fine features of the zone, have been largely ignored.

Lan and Jorgenson have recently demonstrated that the spatial progression of all temporal statistical moments can be stated as a set of ordinary differential equations [10]. These equations describe how the *temporal* profile of the peak evolves as it is detected at progressive points along the column. The general treatment of temporal statistical moments in this theory relies on the Taylor series expansion of functions that describe migration and dispersion. The goal of the current work is to apply the same mathematical strategy to Blumberg's developments so that the spatial and temporal progression of all spatial statistical moments can also be stated as a set of differential equations. These equations can then be used to describe how the *spatial* profile of the chromatographic zone evolves with respect to time or with respect to its position in the column.

2. Theory

2.1. Statistical moments

The statistical moments considered in this work are determined by measuring the spatial profile of concentration at a given *detection time* t . Please note that the detection time is the independent variable, i.e. it is the time chosen to observe the spatial profile of the zone. All statistical moments are thus implicit functions of the detection time. Let us assume that all statistical moments are bounded (Appendix A).

2.1.1. Zeroth moment

The zeroth moment μ_0 is given by [11]

$$\mu_0 \equiv \int_{-\infty}^{\infty} c(x, t) dx \quad (4)$$

where c is the one-dimensional concentration of solute, i.e. amount of solute per length of column. All remaining instances of concentration in this manuscript are in the context of one dimension. The zeroth moment can thus be interpreted as the total amount of a solute in the system.

2.1.2. First normalized moment

The first normalized moment μ_1 is given by [11]

$$\mu_1 \equiv \frac{1}{\mu_0} \int_{-\infty}^{\infty} xc(x, t) dx \quad (5)$$

which can be interpreted as the average distance traveled by the solute by the detection time. Let us also denote the first normalized moment as the *spatial centroid* z :

$$z \equiv \mu_1 \quad (6)$$

The time necessary for the spatial centroid to reach the detector is nearly equal to the retention time in almost all practical cases. (Retention time is usually defined as the time corresponding to the peak's maximum signal at the end of the column.)

2.1.3. Normalized central moments

The n -th normalized central moment μ_n is given by [11]

$$\bar{\mu}_n \equiv \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x - z)^n c(x, t) dx \quad (7)$$

Note that the zeroth and first normalized *central* moments are constants:

$$\bar{\mu}_0 = 1 \quad (8)$$

$$\bar{\mu}_1 = 0 \quad (9)$$

These quantities should not be confused with the zeroth moment and first normalized moment (centroid), as given by Eqs. (4) and (5), respectively. In accordance with convention, we may denote the second normalized central moment as the spatial zone variance σ^2 :

$$\sigma^2 \equiv \bar{\mu}_2 \quad (10)$$

2.2. Net rate of migration

When there is a spatial gradient of the diffusion coefficient, one side of the zone broadens more rapidly than the other side. This asymmetric dispersion of the zone modifies its spatial centroid and thus contributes to the velocity of the spatial centroid. Blumberg and Berger have shown that such a spatial gradient of the diffusion coefficient contributes to the net velocity u of the solute by [3]

$$u(x, s) \equiv v(x, s) + \frac{\partial D}{\partial x}(x, s) \quad (11)$$

Let us assume that the net velocity is positive, bounded, continuously infinitely differentiable in space (i.e. everywhere differentiable at any order with respect to space), and independent of concentration (i.e. the chromatographic medium is linear). Incorporating Eq. (11) into Eq. (2) yields Eq. (3)

$$\frac{\partial c}{\partial s}(x, s) = \frac{\partial^2 Dc}{\partial x^2}(x, s) - \frac{\partial uc}{\partial x}(x, s) \quad (12)$$

2.3. Relationship between diffusion coefficient and local HETP

The modern definition of local HETP (local plate height) H is given by Blumberg [2]:

$$H(x, s) \equiv \lim_{\sigma^2 \rightarrow 0} \frac{d\sigma^2}{dz} \quad (13)$$

where σ^2 is the spatial variance of a zone if it were located at x at time s . The local HETP is the spatial rate at which the variance of a zone would increase if it were injected as a delta function at position x at time s . Such a zone is infinitesimally wide, so its rate of broadening is unaffected by spatial gradients of retention. The local HETP can thus be interpreted as the sum of all band-broadening sources other than that arising from spatial variations of retention [6].

Based on Eq. (13), it can be derived that (Appendix B)

$$D = \frac{H(x, s) u(x, s)}{2} \quad (14)$$

which is the relationship between local HETP and diffusion coefficient that has been used previously [2]. Let us assume that local HETP and net solute velocity are known functions, so that the diffusion coefficient is also a known function. Let us also assume that the diffusion coefficient is positive, bounded, continuously infinitely differentiable in space, and independent of concentration.

2.4. Temporal rates of statistical moment change

The progression of a statistical moment is completely specified by the initial value of the moment and the rate at which the moment changes. Finding convenient expressions for the temporal rates of statistical moment change thus provides a foundation for the prediction of statistical moments.

2.4.1. First normalized moment

The rate at which the spatial centroid increases with detection time is equivalent to the concentration-weighted average of net velocities [2]:

$$\frac{dz}{dt} = \frac{1}{\mu_0} \int_{-\infty}^{\infty} u(x, t) c(x, t) dx \quad (15)$$

If the function u can be accurately expanded about $x=z$ as a Taylor series, Eq. (15) can be restated in terms of normalized central moments (Appendix C):

$$\begin{aligned} \frac{dz}{dt} &= \sum_{m=0}^{\infty} \frac{\bar{\mu}_m}{m!} \cdot \frac{\partial^m u}{\partial x^m}(z, t) \\ &= u(z, t) + 0 + \frac{\bar{\mu}_2}{2} \cdot \frac{\partial^2 u}{\partial x^2}(z, t) + \frac{\bar{\mu}_3}{6} \\ &\quad \cdot \frac{\partial^3 u}{\partial x^3}(z, t) + \dots \end{aligned} \quad (16)$$

This equation cannot be solved alone because the normalized central moments are unknown functions of the detection time.

2.4.2. Normalized central moments

The rate at which a normalized central moment changes with respect to detection time is (Appendix D)

$$\begin{aligned} \frac{d\bar{\mu}_n}{dt} = & -n\bar{\mu}_{n-1} \frac{dz}{dt} + \frac{n(n-1)}{2\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-2} \\ & \times H(x, t) u(x, t) c(x, t) dx \\ & + \frac{n}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-1} u(x, t) c(x, t) dx \end{aligned} \quad (17)$$

Since a factor of n exists in each term on the right hand side (rhs), the zeroth normalized central moment is unchanged with the progress of time, which is consistent with Eq. (8). For the first normalized central moment, a factor of $n-1$ eliminates the second term, and the first and third terms cancel via Eq. (15). Thus, the first normalized central moment also remains unchanged with the progress of time, which is consistent with Eq. (9).

If the functions Hu and u can be accurately expanded about $x=z$ into a Taylor series, Eq. (17) can be restated in terms of normalized central moments (Appendix E):

$$\begin{aligned} \frac{d\bar{\mu}_n}{dt} = & -n\bar{\mu}_{n-1} \frac{dz}{dt} + \frac{n(n-1)}{2} \sum_{m=0}^{\infty} \frac{\bar{\mu}_{m+n-2}}{m!} \\ & \cdot \frac{\partial^m Hu}{\partial x^m}(z, t) + n \sum_{m=0}^{\infty} \frac{\bar{\mu}_{m+n-1}}{m!} \cdot \frac{\partial^m u}{\partial x^m}(z, t) \end{aligned} \quad (18)$$

The rate of change in the n -th normalized central moment can thus be written for any given n . The collection of all such equations ($0 \leq n < \infty$) can be written in matrix form:

$$\begin{pmatrix} d\bar{\mu}_0/dt \\ d\bar{\mu}_1/dt \\ d\bar{\mu}_2/dt \\ \vdots \end{pmatrix} = \begin{pmatrix} L_{00} & L_{01} & L_{02} & \cdots \\ L_{10} & L_{11} & L_{12} & \cdots \\ L_{20} & L_{21} & L_{22} & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix} \begin{pmatrix} \bar{\mu}_0 \\ \bar{\mu}_1 \\ \bar{\mu}_2 \\ \vdots \end{pmatrix} \quad (19)$$

or, simply,

$$\boldsymbol{\mu}' = \mathbf{L}\boldsymbol{\mu} \quad (20)$$

where

$$L_{nk} = A_{nk} + B_{nk} + C_{nk} \quad (21)$$

$$A_{nk} = \begin{cases} -n \frac{dz}{dt}, & k-n = -1 \\ 0, & k-n \neq -1 \end{cases} \quad (22)$$

$$B_{nk} = \begin{cases} \frac{1}{2} \cdot \frac{n(n-1)}{(k-n+2)!} \cdot \frac{\partial^{(k-n+2)} Hu}{\partial x^{(k-n+2)}}(z, t), & k-n \geq -2 \\ 0, & k-n < -2 \end{cases} \quad (23)$$

$$C_{nk} = \begin{cases} \frac{n}{(k-n+1)!} \cdot \frac{\partial^{(k-n+1)} u}{\partial x^{(k-n+1)}}(z, t), & k-n \geq -1 \\ 0, & k-n < -1 \end{cases} \quad (24)$$

Eqs. (22), (23), and (24) respectively represent the first, second, and third terms on the rhs of Eq. (18). Note that the second row ($n=1$) of matrix \mathbf{L} contains non-zero elements, but the dot product of this row and the vector $\boldsymbol{\mu}$ is always zero (Appendix E). We may thus replace all elements in the second row with zeroes to achieve the same result. Similarly, the second column ($k=1$) contains non-zero elements, but these elements are multiplied by the first normalized central moment, which is zero (Eq. (9)), when the dot product is taken. We may thus also replace the elements in the second column with zeroes:

$$L_{nk} = \begin{cases} A_{nk} + B_{nk} + C_{nk}, & n \neq 1 \text{ and } k \neq 1 \\ 0, & n = 1 \text{ or } k = 1 \end{cases} \quad (25)$$

For the remainder of this work, we will use this equation instead of Eq. (21) to calculate elements L_{nk} .

2.4.3. Ordinary differential equation system

Eq. (19) describes the rates of change for all normalized central moments, but this differential equation system is not complete because the matrix is a function of two parameters: the spatial centroid and the detection time. Eq. (16) relates the spatial centroid to the detection time in terms of all normalized central moments, so the combination of Eqs. (16) and (19) constitutes a complete differential equation system. It is interesting to note that this differential equation system is nonlinear with respect to statistical moments, despite that it describes a chemically linear chromatographic process.

2.5. Simplifications based on spatial moderation

The basic strategies of simplifying Eqs. (16) and (19) rely on the assumption of *spatial moderation* [3], i.e. any spatial variation in either Hu or u is sufficiently gradual such that the sum of low-order

terms in the Taylor series accurately represents the original function in the domain about the zone.

2.5.1. Finite system approximation

The system of equations can be reduced to a finite size by truncating references to normalized central moments of orders greater than a given value. This task is easily accomplished by limiting the dimensions of the matrix and vectors in Eq. (19) to a finite value r , so that the matrix has dimensions of $r \times r$ and the vectors have a dimension of r . Accordingly, Eq. (16) must also be truncated so that only the first r terms (up to order $r-1$) in the Taylor series are used. For example, at a dimension size of $r=5$, Eqs. (16) and (19) become

$$\frac{dz}{dt} = u(z, t) + 0 + \frac{\bar{\mu}_2}{2} \cdot \frac{\partial^2 u}{\partial x^2}(z, t) + \frac{\bar{\mu}_3}{6} \cdot \frac{\partial^3 u}{\partial x^3}(z, t) + \frac{\bar{\mu}_4}{24} \cdot \frac{\partial^4 u}{\partial x^4}(z, t) \quad (26)$$

$$\begin{pmatrix} d\bar{\mu}_0/dt \\ d\bar{\mu}_1/dt \\ d\bar{\mu}_2/dt \\ d\bar{\mu}_3/dt \\ d\bar{\mu}_4/dt \end{pmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ Hu & 0 & \frac{1}{2} \cdot \frac{\partial^2 Hu}{\partial x^2} + 2 \frac{\partial u}{\partial x} & \frac{1}{6} \cdot \frac{\partial^3 Hu}{\partial x^3} + \frac{\partial^2 u}{\partial x^2} & \frac{1}{24} \cdot \frac{\partial^4 Hu}{\partial x^4} + \frac{1}{3} \cdot \frac{\partial^3 u}{\partial x^3} \\ 0 & 0 & -3 \frac{dz}{dt} + 3 \frac{\partial Hu}{\partial x} + 3u & 3 \cdot \frac{\partial^2 Hu}{\partial x^2} + 3 \frac{\partial u}{\partial x} & \frac{1}{2} \cdot \frac{\partial^3 Hu}{\partial x^3} + 3 \cdot \frac{\partial^2 u}{\partial x^2} \\ 0 & 0 & 6Hu & -4 \frac{dz}{dt} + 6 \frac{\partial Hu}{\partial x} + 4u & 3 \cdot \frac{\partial^2 Hu}{\partial x^2} + 4 \frac{\partial u}{\partial x} \end{bmatrix} \times \begin{pmatrix} \bar{\mu}_0 \\ \bar{\mu}_1 \\ \bar{\mu}_2 \\ \bar{\mu}_3 \\ \bar{\mu}_4 \end{pmatrix} \quad (27)$$

In Eq. (27), the functions Hu , u , and their partial derivatives are evaluated at (z, t) .

A finite system approximation eliminates the fewest possible terms to make the system theoretically solvable for a given dimension size r , so the solutions to these systems are presumably the most accurate for that dimension size. This accuracy, however, comes at the cost of complexity. Unless further simplifications are made, it is usually very difficult to solve these systems analytically. Nonetheless, numerical solutions to these systems can pro-

vide an important utility by serving as references to test the accuracy of further simplifications.

2.5.2. Low-order approximation

Eqs. (16) and (19) may be further simplified by excluding terms that have derivatives above a certain order h . Let us denote the resulting equations as h -th-order approximations.

2.5.3. Linear equation system approximation

The first-order approximation of Eq. (16) is

$$\frac{dz}{dt} = u(z, t) \quad (28)$$

This equation indicates that the progression of the spatial centroid, under spatially moderate conditions, is relatively insensitive to the second- and higher-order normalized central moments. The solution to this ordinary differential equation gives an estimate of the spatial centroid as a function of detection time. By using this function to relate the two parameters of matrix \mathbf{L} , Eq. (19) becomes a linear differential equation system. For example, Eq. (27) can be approximated as a linear equation system by using Eq. (28). Furthermore, substitution of Eq. (28) into elements L_{32} (fourth row, third column) and L_{43} (fifth row, fourth column) of Eq. (27) gives a cancellation of terms:

$$\begin{pmatrix} d\bar{\mu}_0/dt \\ d\bar{\mu}_1/dt \\ d\bar{\mu}_2/dt \\ d\bar{\mu}_3/dt \\ d\bar{\mu}_4/dt \end{pmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ Hu & 0 & \frac{1}{2} \cdot \frac{\partial^2 Hu}{\partial x^2} + 2 \frac{\partial u}{\partial x} & \frac{1}{6} \cdot \frac{\partial^3 Hu}{\partial x^3} + \frac{\partial^2 u}{\partial x^2} & \frac{1}{24} \cdot \frac{\partial^4 Hu}{\partial x^4} + \frac{1}{3} \cdot \frac{\partial^3 u}{\partial x^3} \\ 0 & 0 & 3 \frac{\partial Hu}{\partial x} & \frac{3}{2} \cdot \frac{\partial^2 Hu}{\partial x^2} + 3 \frac{\partial u}{\partial x} & \frac{1}{2} \cdot \frac{\partial^3 Hu}{\partial x^3} + \frac{3}{2} \cdot \frac{\partial^2 u}{\partial x^2} \\ 0 & 0 & 6Hu & \frac{\partial Hu}{\partial x} & 3 \cdot \frac{\partial^2 Hu}{\partial x^2} + 4 \frac{\partial u}{\partial x} \end{bmatrix} \times \begin{pmatrix} \bar{\mu}_0 \\ \bar{\mu}_1 \\ \bar{\mu}_2 \\ \bar{\mu}_3 \\ \bar{\mu}_4 \end{pmatrix} \quad (29)$$

In general, these cancellations occur in elements L_{nk} , where $k-n = -1$.

2.5.4. Triangular matrix approximation

All elements above the main diagonal ($k - n > 0$) in matrix \mathbf{L} contain only second- or higher-order derivatives of Hu and u . When the chromatographic system is spatially moderate, these elements can be approximated as zero, resulting in a triangular matrix. For example, Eq. (29) becomes

$$\begin{pmatrix} d\bar{\mu}_0/dt \\ d\bar{\mu}_1/dt \\ d\bar{\mu}_2/dt \\ d\bar{\mu}_3/dt \\ d\bar{\mu}_4/dt \end{pmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ Hu & 0 & \frac{1}{2} \cdot \frac{\partial^2 Hu}{\partial x^2} + 2 \frac{\partial u}{\partial x} & 0 & 0 \\ 0 & 0 & 3 \frac{\partial Hu}{\partial x} & \frac{3}{2} \cdot \frac{\partial^2 Hu}{\partial x^2} + 3 \frac{\partial u}{\partial x} & 0 \\ 0 & 0 & 6Hu & 6 \frac{\partial Hu}{\partial x} & 3 \frac{\partial^2 Hu}{\partial x^2} + 4 \frac{\partial u}{\partial x} \end{bmatrix} \times \begin{pmatrix} \bar{\mu}_0 \\ \bar{\mu}_1 \\ \bar{\mu}_2 \\ \bar{\mu}_3 \\ \bar{\mu}_4 \end{pmatrix} \quad (30)$$

A linear differential equation system with a triangular matrix can be solved much more easily because the differential equations of the system are solved sequentially instead of simultaneously. Note that a first-order approximation of the matrix \mathbf{L} always results in a triangular matrix. For example, the first-order approximation of Eq. (27) is

$$\begin{pmatrix} d\bar{\mu}_0/dt \\ d\bar{\mu}_1/dt \\ d\bar{\mu}_2/dt \\ d\bar{\mu}_3/dt \\ d\bar{\mu}_4/dt \end{pmatrix} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ Hu & 0 & 2 \frac{\partial u}{\partial x} & 0 & 0 \\ 0 & 0 & 3 \frac{\partial Hu}{\partial x} & 3 \frac{\partial u}{\partial x} & 0 \\ 0 & 0 & 6Hu & 6 \frac{\partial Hu}{\partial x} & 4 \frac{\partial u}{\partial x} \end{bmatrix} \begin{pmatrix} \bar{\mu}_0 \\ \bar{\mu}_1 \\ \bar{\mu}_2 \\ \bar{\mu}_3 \\ \bar{\mu}_4 \end{pmatrix} \quad (31)$$

2.5.5. Spatially invariant systems

In spatially uniform chromatographic systems, the local HETP and net velocity functions may vary in

time, but they do not vary in space. Let us denote these systems as being *spatially invariant*. The theoretical treatment of spatially invariant systems is greatly simplified because the spatial derivatives of Hu and u are zero. As a result, Eq. (28) is exact for these systems:

$$dz = u(t) dt \quad (32)$$

Eq. (18) is simplified to (Appendix G)

$$d\bar{\mu}_n = \frac{n(n-1)}{2} \bar{\mu}_{n-2} H(t) u(t) dt \quad (33)$$

Statistical moments can thus be calculated by integration.

Only a few practical systems of column chromatography are well approximated as being spatially invariant [3]. Examples include isocratic liquid chromatography with relatively low pressure gradients and isothermal gas chromatography with relatively low pressure gradients. Most practical systems of isocratic liquid chromatography and isothermal gas chromatography have relatively steep pressure gradients, which can lead to pressure-induced retention variations [6,12–16], frictional heating of liquid mobile phase [17,18], and decompression of gaseous mobile phase [19]. All of these effects produce spatial variations of solute velocity.

2.6. Spatial progression of normalized central moments

Solving the system of differential equations given by Eqs. (16) and (19) (or any of their simplifications) yields the spatial centroid and normalized central moments as implicit functions of detection time. Normalized central moments, however, are conventionally given as functions of the spatial centroid, not detection time. Since the relationship between the spatial centroid z and detection time t is already given in the solution, the conversion of independent variables for the normalized central moments relies only upon finding the inverse of $z(t)$:

$$\bar{\mu}_n(z) = \bar{\mu}_n(t(z)) \quad (34)$$

Alternatively, Eq. (19) can be restated so that the spatial centroid is the independent variable:

$$\begin{pmatrix} d\bar{\mu}_0/dz \\ d\bar{\mu}_1/dz \\ d\bar{\mu}_2/dz \\ \vdots \end{pmatrix} = \frac{dt}{dz} \begin{pmatrix} L_{00} & L_{01} & L_{02} & \cdots \\ L_{10} & L_{11} & L_{12} & \cdots \\ L_{20} & L_{21} & L_{22} & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix} \begin{pmatrix} \bar{\mu}_0 \\ \bar{\mu}_1 \\ \bar{\mu}_2 \\ \vdots \end{pmatrix} \quad (35)$$

The solution to Eqs. (16) and (35) gives the spatial centroid as an implicit function of detection time and the normalized central moments as implicit functions of the spatial centroid. All of the simplifications described earlier can also be applied to Eq. (35). For example, Eq. (3) can be derived from Eq. (35) based on these simplifications. (Appendix H).

3. Discussion

The limitations of spatial statistical moment theory are implicitly given by the assumptions used in its derivation. Since many of the assumptions used in the work are nearly always accurate in practical chromatography, only the assumptions that may have important practical implications are discussed below.

3.1. Spatial moderation

In order to solve the system of differential equations given by Eq. (16) and (19), spatial moderation is always necessary. Unfortunately, there are a few practical systems of chromatography that are not spatially moderate [4]. One example is step gradient elution liquid chromatography, where the sudden change in mobile phase composition makes the system both spatially and temporally immoderate. Another example is a system where two different columns are connected in series. Also note that junctions in a chromatographic system (e.g. between a column and connective tubing) are also spatially immoderate, so the requirement of spatial moderation prohibits a chromatographic system from being modeled in its entirety.

3.2. Conversion to temporal statistical moments

The spatial centroid and spatial variance are easily

converted into their temporal counterparts. The inverse of $z(t)$, which is $t(z)$, is good approximation for the temporal centroid. In turn, the temporal centroid evaluated at the detector position is a good approximation for the retention time. The spatial variance is easily converted to temporal variance τ^2 by the following well-known approximation:

$$\tau^2 = \sigma^2/v^2(z, t) \quad (36)$$

Unfortunately, modern chromatographic theory cannot convert higher-order ($n > 2$) spatial statistical moments into temporal statistical moments unless the medium is both spatially and temporally invariant [10]. This limitation of spatial statistical moment theory is serious because almost all chromatographic detectors measure the zone's temporal profile, not spatial profile. Nonetheless, future developments in theory may permit conversions between high-order spatial and temporal statistical moments.

3.3. High efficiency

Since chromatographic dispersion is modeled as effective diffusion process in this theory, high efficiencies are necessary to ensure that individual dispersion sources behave in a diffusion-like manner [1]. High efficiencies (> 100) are achieved in relatively short distances ($< 2\%$ of the column length) in modern chromatographic systems, so this requirement is not very prohibitive.

3.4. Radial homogeneity

Using a one-dimensional model of chromatography obviously requires the assumption that the system has radial homogeneity, but this quality is not perfectly exhibited in real chromatographic systems. Deficiencies in radial homogeneity arise from effects such as poorly swept void volumes or radial variations of flow velocity and efficiency. These effects contribute to zone asymmetry [20,21] in a manner that cannot be included in the theory.

It is also known that radial variations of flow velocity and efficiency contribute to the broadening of zones, and this effect is easily incorporated into

the model by using an effective diffusion coefficient that includes this source of broadening [22].

3.5. Linearity of the chromatographic medium.

The local HETP and net velocity functions are assumed to be independent of the concentration of any solute. This assumption allows the theory to be applied to the individual components of a mixture, and it is also necessary so that the functions Hu and u and their spatial derivatives are known functions of space, which is necessary to solve Eq. (16) and (19). Linearity of the medium is generally a fair approximation in analytical chromatography, where column overloading is actively avoided.

4. Nomenclature

A_{nk}	the component of L_{nk} that accounts for the shift in the spatial centroid
B_{nk}	the component of L_{nk} that accounts for dispersion
c	one-dimensional concentration
C_{nk}	the component of L_{nk} that accounts for net migration
D	Fick diffusion coefficient
H	local HETP
j	one-dimensional flux
\mathbf{L}	a matrix that relates $\boldsymbol{\mu}$ to $\boldsymbol{\mu}'$
L_{nk}	the element of \mathbf{L} in row $n+1$, column $k+1$
$\boldsymbol{\mu}$	the vector of spatial normalized central moments
$\boldsymbol{\mu}'$	the derivative of $\boldsymbol{\mu}$ with respect to detection time
μ_0	spatial zeroth moment
μ_1	spatial first normalized moment
$\bar{\mu}_n$	spatial n -th normalized central moment
r	dimension size
s	time
σ^2	spatial variance
t	detection time
τ^2	temporal variance
u	net solute velocity
v	solute velocity
x	one-dimensional spatial coordinate
z	spatial centroid

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Appendix A. Implications of bounded normalized central moments

If all normalized central moments are bounded, the integrand of Eq. (7) must approach zero for large magnitudes of x :

$$\lim_{|x| \rightarrow \infty} (x-z)^n c(x, t) = 0 \quad (\text{A.1})$$

for any order n .

The spatial derivative of Eq. (A.1) is

$$\lim_{|x| \rightarrow \infty} \left((x-z)^n \frac{dc(x, t)}{dx} + n(x-z)^{n-1} c(x, t) \right) = 0 \quad (\text{A.2})$$

The second term in the limit is zero owing to Eq. (A.1); the elimination results in

$$\lim_{|x| \rightarrow \infty} (x-z)^n \frac{dc(x, t)}{dx} = 0 \quad (\text{A.3})$$

for any order n .

It is theoretically possible to have an unbounded normalized central moment for a zone [2]. Consider, for example, a concentration profile $c(x)$ that converges *rationaly* to zero:

$$c(x) = \frac{1}{(|x| + 1)^m} \quad (\text{A.4})$$

where $m > 2$. The zeroth moment (peak area) and first normalized moment (centroid) for this function are always bounded. Nonetheless, this function does not satisfy Eq. (A.1) for $n \geq m$, so unbounded normalized central moments indeed exist for this zone. Fortunately, virtually all real chromatographic peaks converge *exponentially*, not *rationaly*, to zero, so Eq. (A.1) is almost always valid in practical chromatography.

Appendix B. Relationship between local HETP and diffusion coefficient

The temporal rate of spatial variance change can be stated as [3]

$$\begin{aligned} \frac{d\sigma^2}{dt} &= \frac{2}{\mu_0} \int_{-\infty}^{\infty} D(x, t) c(x, t) dx \\ &+ \frac{2}{\mu_0} \int_{-\infty}^{\infty} (x - z) u(x, t) c(x, t) dx \end{aligned} \quad (\text{B.1})$$

The Taylor series of D and u about $x = z$ are

$$D(x, t) = \sum_{m=0}^{\infty} \frac{(x - z)^m}{m!} \cdot \frac{\partial^m D}{\partial x^m}(z, t) \quad (\text{B.2})$$

$$u(x, t) = \sum_{m=0}^{\infty} \frac{(x - z)^m}{m!} \cdot \frac{\partial^m u}{\partial x^m}(z, t) \quad (\text{B.3})$$

Substitution of these equations into Eq. (B.1) and rearrangement yields

$$\begin{aligned} \frac{d\sigma^2}{dt} &= 2 \sum_{m=0}^{\infty} \frac{1}{m!} \cdot \frac{\partial^m D}{\partial x^m}(z, t) \\ &\cdot \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x - z)^m c(x, t) dx + 2 \sum_{m=0}^{\infty} \frac{1}{m!} \\ &\cdot \frac{\partial^m u}{\partial x^m}(z, t) \cdot \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x - z)^{m+1} c(x, t) dx \end{aligned} \quad (\text{B.4})$$

The definition of normalized central moments (Eq. (7)) can then be applied to give

$$\begin{aligned} \frac{d\sigma^2}{dt} &= 2 \sum_{m=0}^{\infty} \frac{\bar{\mu}_m}{m!} \cdot \frac{\partial^m D}{\partial x^m}(z, t) + 2 \sum_{m=0}^{\infty} \frac{\bar{\mu}_{m+1}}{m!} \\ &\cdot \frac{\partial^m u}{\partial x^m}(z, t) \end{aligned} \quad (\text{B.5})$$

For an infinitesimally wide zone, the first- and higher-order normalized central moments are all zero, so taking the limit of very narrow zones leaves

$$\begin{aligned} \lim_{\sigma^2 \rightarrow 0} \frac{d\sigma^2}{dt} &= \lim_{\sigma^2 \rightarrow 0} \frac{d\sigma^2}{\sigma^2} \cdot \frac{d\sigma^2}{dz} \cdot \frac{dz}{dt} = H(z, t) \lim_{\sigma^2 \rightarrow 0} \frac{dz}{dt} \\ &= 2D(z, t) \end{aligned} \quad (\text{B.6})$$

In the limit of infinitesimally wide zones, Eq. (16)

indicates that the dz/dt can be replaced by u . The resulting equation can be rearranged into Eq. (14).

Appendix C. Incorporation of Taylor series into the temporal rate of spatial centroid change

Substitution of Eq. (B.3) into Eq. (15) and rearrangement yields

$$\begin{aligned} \frac{dz}{dt} &\approx \frac{1}{\mu_0} \int_{-\infty}^{\infty} \left(\sum_{m=0}^{\infty} \frac{(x - z)^m}{m!} \cdot \frac{\partial^m u}{\partial x^m}(z, t) \right) c(x, t) dx \\ &= \sum_{m=0}^{\infty} \frac{1}{m!} \cdot \frac{\partial^m u}{\partial x^m}(z, t) \cdot \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x - z)^m c(x, t) dx \end{aligned} \quad (\text{C.1})$$

The definition of normalized central moments (Eq. (7)) can then be applied to give Eq. (16).

Appendix D. Temporal rate of normalized central moment change

The derivative of a normalized central moment (Eq. (7)) with respect to detection time is

$$\begin{aligned} \frac{d\bar{\mu}_n}{dt} &= \frac{-n}{\mu_0} \cdot \frac{dz}{dt} \int_{-\infty}^{\infty} (x - z)^{n-1} c(x, t) dx \\ &+ \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x - z)^n \frac{dc(x, t)}{dt} dx \end{aligned} \quad (\text{D.1})$$

The first integral can be simplified by applying the definition of normalized central moments, and Eq. (12) can be substituted into the second integral:

$$\begin{aligned} &= -n\bar{\mu}_{n-1} \frac{dz}{dt} + \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x - z)^n \\ &\times d \left(\frac{dD(x, t)c(x, t)}{dx} - u(x, t)c(x, t) \right) \end{aligned} \quad (\text{D.2})$$

Integration by parts can be applied to the integral:

$$\begin{aligned}
&= -n\bar{\mu}_{n-1} \frac{dz}{dt} + \frac{1}{\mu_0} \\
&\quad \times \left((x-z)^n \left(\frac{dD(x,t)c(x,t)}{dx} - u(x,t)c(x,t) \right) \right) \Big|_{x=-\infty}^{x=\infty} \\
&\quad - \frac{n}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-1} \left(\frac{dD(x,t)c(x,t)}{dx} - u(x,t)c(x,t) \right) dx
\end{aligned} \tag{D.3}$$

The second term evaluates to zero owing to Eq. (A.1) and Eq. (A.3). The integral can be expanded:

$$\begin{aligned}
&= -n\bar{\mu}_{n-1} \frac{dz}{dt} \\
&\quad - \frac{n}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-1} d(D(x,t)c(x,t)) \\
&\quad + \frac{n}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-1} u(x,t)c(x,t) dx
\end{aligned} \tag{D.4}$$

Integration by parts can be applied to the first integral:

$$\begin{aligned}
&= -n\bar{\mu}_{n-1} \frac{dz}{dt} - \frac{n}{\mu_0} \left((x-z)^{n-1} D(x,t)c(x,t) \right) \Big|_{x=-\infty}^{x=\infty} \\
&\quad + \frac{n(n-1)}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-2} D(x,t)c(x,t) dx \\
&\quad + \frac{n}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-1} u(x,t)c(x,t) dx
\end{aligned} \tag{D.5}$$

The second term evaluates to zero owing to Eq. (A.1). The diffusion coefficient D can be stated in terms of local HETP (Eq. (14)), resulting in Eq. (17).

Appendix E. Incorporation of Taylor series into the temporal rate of normalized central moment change

The Taylor series of Hu about $x=z$ is

$$H(x,t)u(x,t) \approx \sum_{m=0}^{\infty} \frac{(x-z)^m}{m!} \cdot \frac{\partial^m Hu}{\partial x^m}(z,t) \tag{E.1}$$

Substitution of this equation and Eq. (B.3) into Eq. (17) and rearrangement yields

$$\begin{aligned}
\frac{d\bar{\mu}_n}{dt} &\approx -n\bar{\mu}_{n-1} \frac{dz}{dt} + \frac{n(n-1)}{2} \sum_{m=0}^{\infty} \frac{1}{m!} \cdot \frac{\partial^m Hu}{\partial x^m}(z,t) \\
&\quad \cdot \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{m+n-2} c(x,t) dx \\
&\quad + n \sum_{m=0}^{\infty} \frac{1}{m!} \cdot \frac{\partial^m u}{\partial x^m}(z,t) \cdot \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{m+n-1} c(x,t) dx
\end{aligned} \tag{E.2}$$

The definition of normalized central moments (Eq. (7)) can then be applied to give Eq. (18).

Appendix F. Dot product of L_{1k} and μ is zero

The dot product of the second row ($n=1$) of matrix \mathbf{L} and the vector μ gives the change in the first normalized central moment:

$$\frac{d\mu_1}{dt} = -\frac{dz}{dt} + \sum_{k=0}^{\infty} \frac{\bar{\mu}_k}{k!} \cdot \frac{\partial^k u}{\partial x^k}(z,t) \tag{F.1}$$

The first term on the rhs cancels the summation via Eq. (16), indicating that the first normalized central moment is a constant, which is in agreement with Eq. (9).

Appendix G. Temporal rate of normalized central moment change in spatially invariant systems

If the local HETP and net velocity are functions only of time, Eq. (17) can be restated as

$$\begin{aligned}
\frac{d\bar{\mu}_n}{dt} &= -n\bar{\mu}_{n-1} \frac{dz}{dt} + \frac{n(n-1)}{2} \\
&\quad \cdot \frac{H(t)u(t)}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-2} c(x,t) dx \\
&\quad + nu(t) \frac{1}{\mu_0} \int_{-\infty}^{\infty} (x-z)^{n-1} c(x,t) dx
\end{aligned} \tag{G.1}$$

applying the definition of normalized central moments (Eq. (7)) allows the first term on the rhs to cancel the third term, which leaves Eq. (33).

Appendix H. Eq. (3) Is a special case of Eq. (35)

At a dimension size of $r=3$, Eq. (35) can be restated as:

$$\frac{d\sigma^2}{dz} = \frac{dt}{dz} \left(H(z, t)u(z, t) + \frac{\sigma^2}{2} \cdot \frac{\partial^2 Hu}{\partial x^2}(z, t) + 2\sigma^2 \frac{\partial u}{\partial x}(z, t) \right) \quad (\text{H.1})$$

The linear equation system approximation permits the replacement of dz/dt with $u(z, t)$ via Eq. (28). Upon distribution,

$$\frac{d\sigma^2}{dz} = H(z, t) + \frac{\sigma^2}{2u(z, t)} \cdot \frac{\partial^2 Hu}{\partial x^2}(z, t) + \frac{2\sigma^2}{u(z, t)} \frac{\partial u}{\partial x}(z, t) \quad (\text{H.2})$$

Expansion of the second partial derivative of Hu gives us

$$\frac{d\sigma^2}{dz} = H(z, t) + \frac{\sigma^2}{2u(z, t)} \cdot \left(H \frac{\partial^2 u}{\partial x^2}(z, t) + 2 \frac{\partial H}{\partial x} \cdot \frac{\partial u}{\partial x}(z, t) + u \frac{\partial^2 H}{\partial x^2}(z, t) \right) + \frac{2\sigma^2}{u(z, t)} \cdot \frac{\partial u}{\partial x}(z, t) \quad (\text{H.3})$$

A first-order approximation of this equation simplifies to Eq. (3).

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